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ENHANCING ATTENTION IN NEURODEGENERATIVE DISEASES: CURRENT THERAPIES AND FUTURE DIRECTIONS

Abstract

We all experience at least occasional lapses in attention but in some neurological conditions, loss of attention is pervasive and debilitating. Treating deficits in attention first requires an understanding of the neurobiology of attention, which we now understand to be a set of different cognitive processes. Cholinesterase inhibitors are already established as effective attentional enhancers used in the treatment of certain dementias. Other stimulant agents such as modafinil, amphetamine and methylphenidate have demonstrated limited success in healthy individuals where attention is already optimal and clinical trials in patients with neurological disease are sparse. Dietary and lifestyle changes are gaining increasing prominence, as are experimental treatments such as deep brain stimulation and transcranial magnetic stimulation. As the therapeutic arsenal widens, clinicians will be able to match specific treatments to selective deficits in attention, giving patients a tailored management plan. Here we review common diseases that impair attention and emphasise how an understanding of attentional processing within the brain might lead to improved therapeutic strategies.

Keywords

Alerting network • Attention network • Caffeine • Executive network • Meditation • Neurodegeneration

Attention facilitates cognitive functions such as memory, language, problem solving, and perception optimal for goal-oriented behaviour. The ambient environment is a constant source of sensory stimulation in the form of sights, sounds, smells, temperature, and touch. To process all these stimuli continuously would be unnecessarily demanding upon a finite cognitive resource, as much of the information would be irrelevant to the task at hand. A crucial cognitive skill for survival is the ability to selectively process or disregard information from the abundance of sensory input enabling goal-directed behaviour to be achieved. The importance of attention is often overlooked as it does not localise anatomically and is therefore difficult to study. However, when impaired, the consequences can be devastating. This is evident in dementia with Lewy bodies, where people can suffer with fluctuations in attention lasting minutes to days rendering them confused and unable to interact with the world around them.

Attention describes a complex interaction of multiple independent systems distributed within the brain [2, 3]. Voluntary “top-down” shifts of attention are goal-directed, driven by information regarding the current task whilst automatic “bottom-up” exogenous influences of attention are stimulus driven [4]. Through both top-down and bottom-up influences, attention allows us to selectively process or inhibit information from the abundance of sensory input over multiple domains [5, 6]. Breakdown of specific brain areas or neurotransmitter systems causes selective disruptions of attentional networks in both healthy aging and disease processes [7]. Thus attention can be considered a bottleneck for cognitive processing [8] – enhance attention and overall brain function can be improved. Here we review the network physiology, common causes of attention dysfunction and discuss recent developments in the field of attention enhancers.


Neurobiology of attention

Anatomical explanations of attention involve three core networks, each with its own characteristic psychological and neuroanatomical properties; the *alerting*, *orienting*, and *executive* networks of attention [9].

Alerting describes the ability to maintain optimal vigilance and performance during a task, which relies on a right hemisphere cortical and subcortical network involving the anterior cingulate cortex as a synchronizing structure [10]. Frontal, thalamic, and parietal regions are particularly active during tasks of alerting attention [2]. The neurotransmitter noradrenaline arising in the locus coeruleus of the brainstem has been implicated in the alerting network, notably in its ability to elevate readiness to respond as a result of an external cue [11-14].

The orienting network is concerned with the ability to align attention to a source of

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sensory input both overtly, in conjunction with eye movements, or covertly, in the absence of eye movements. It contextualises attentional focus so that specific information can be selected when presented with multiple competing sensory stimuli. The orienting of attention uses a network including the superior parietal cortex, temporoparietal cortex, frontal eye fields, pulvinar, and superior colliculus [9, 15]. Furthermore, impairments to orienting tasks were found following lesions to the basal forebrain systems of macaque monkeys [16], implicating these areas in the orienting network. Orienting has been linked to activation of cholinergic pathways [17], supported by research in rat brains that suggest acetylcholine, but not dopamine, is important for orienting tasks [18].

Executive networks are called upon during tasks that require top-down attentional control and the ability to focus attention selectively according to task demands. Tasks involving selective planning, monitoring or inhibition of automatic responses produce subjective reports of mental exertion. During attention that is mentally exerting and conflict monitoring the anterior cingulate cortex is consistently activated [19]. Interestingly, this network may possess higher-level metacognitive properties, in other words, the network might be involved in generating the subjective impression of cognitive effort [20, 21]. It dynamically interacts with primary sensory regions via bottom-up signals, which subsequently enhance top-down modulation of sensory processing via a feedback mechanism [22]. Anatomically, the network of structures involved in executive attentional tasks includes the anterior cingulate cortex [23], the medial frontal cortex [9], lateral ventral prefrontal cortex, and basal ganglia. The influence of the mesocortical dopamine system on these areas implicates the neurotransmitter in executive attention.

When does attention break down?

Attention deficits in health

While individual differences make some people more prone to lapses in attention, age alone is a risk factor for mild attentional decline. Older people are slower to react during alerting tasks [24] and perform slower on executive attention tasks [25], although orienting attention remains preserved with age [26]. There is debate about whether responding slowly to a target stimulus during an alerting task, a defining feature of age-related cognitive decline, is due to alterations in general processing speed or a selective deficit in an attentional domain [27]. However, motor processing speed alone could not explain the executive deficits. Generalised slowing of cognitive processing speed probably represents a decline in the structural integrity of the white matter tracts and loss

of brain volume, both of which progress with advancing age [28].

We all suffer lapses in attention occasionally but there are situations when this can be detrimental. Hence the motivation for cognitive enhancement in healthy people is often when sustained vigilance taxing the alerting network is required, for example students at exam time, soldiers in battle or doctors on call. Prescription stimulant misuse by undergraduate American college students to enhance cognitive performance is well documented [29]. The incidence is estimated to be 3-10% with exam preparation cited as the most common reason [30]. The most commonly misused stimulants were methylphenidate, dextroamphetamine, methamphetamine and modafinil [31]. In cognitively normal individuals stimulants can improve attention, enhance consolidation of recently acquired information, reduce fatigue and the need for sleep [31, 32]. From

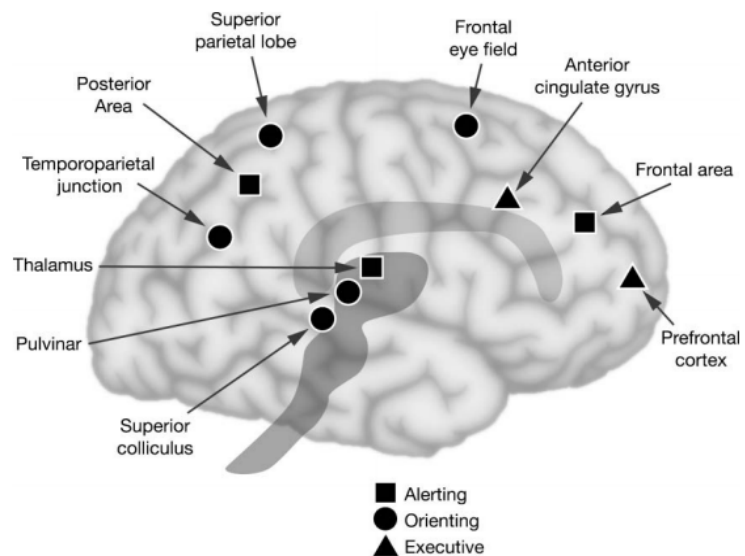


Figure 1. Anatomy of the trinity of attention networks: alerting, orienting, and executive [1].

Terminology		Neurotransmitter systems predominantly implicated	Associated neurological conditions	Common cognitive tests
New	Old			
Alerting network	Sustained attention	Noradrenaline	Narcolepsy	Cognitive reaction time
Orienting network	Selective attention	Cholinergic	Dementia with Lewy bodies, Parkinson's disease dementia	Rapid Serial Visual Presentation paradigm
Executive network	Divided attention	Dopamine	Attention Deficit Hyperactive Disorder	Stroop task, Wisconsin Card Sorting Test

a pharmacological perspective little is known about the long-term side effects of healthy individuals misusing prescription drugs or whether tolerance develops and performance is impaired following withdrawal [32].

Attention deficits in neurological disease

Dementia with Lewy bodies (DLB) is characterised by fluctuations in consciousness leading to daytime somnolence; visual hallucinations and parkinsonism with additional features such as rapid eye movement (REM) sleep behaviour disorder. Parkinson's disease progresses to dementia in up to 80% of cases [33]. These two clinical syndromes differ in the sequence of onset of dementia and parkinsonism, but with progression both syndromes and underlying pathological changes become similar and can be viewed as a continuum rather than dichotomous entities. They are known under the umbrella term Lewy body dementias [34].

Anecdotally, as clinicians we have seen people so profoundly affected by attention fluctuations that they are admitted to hospital with episodes of presumed loss of consciousness and investigated for epilepsy and other conditions. A breakdown in attentional function is thought to underpin the tendency to fluctuations, which may also contribute to the development of visual hallucinations through impaired bottom-up processing of sensory information that allows false data to be sent to the entire cortex and not be recognised as abnormal [35].

People with DLB struggle to attain the minimal activation of alertness needed for both attention and information processing to operate [36]. DLB patients also experience serious difficulties in drawing their attention to new relevant locations, suggesting their orienting attention is impaired [37]. Executive dysfunction is an early, prominent neuropsychological feature [38], thus failure of attention is a particular problem in this group with all networks affected [39]. DLB results from the accumulation of neuronal intracellular aggregates of α -synuclein, which form Lewy bodies, secondary cellular injury, and apoptotic neurodegeneration [40]. Pathologically, the

concentration of Lewy bodies is distributed in the frontal, cingulate and inferior temporal cortex, substantia nigra, locus coeruleus and components of the basal forebrain cholinergic system [41]. The observed deficits in alerting attention correspond to pathology in the locus coeruleus affecting the noradrenergic system; orienting attention deficits correspond to the cholinergic system of the basal forebrain and executive attention deficits correspond to substantia nigra pathology affecting the dopaminergic system [42].

Using medications to enhance attention in this population can consequentially improve other cognitive domains such as memory as well as overall cognitive function. The net effect to an individual is an improved quality of life and maintenance of independence a few years longer than previously possible [43]. Across a population of people with dementia this will significantly reduce care costs, potentially saving billions of pounds each year. The extensive cholinergic depletion in DLB may explain [38] improvement with cholinesterase inhibitor therapy [44], which has been licenced (specifically Rivastigmine) for Parkinson's disease dementia since 2006 [45] and is used in DLB on the basis of the same underlying pathology. There is no established effective therapy to improve daytime somnolence, which has a significant impact on quality of life, with mixed results from trials exploring methylphenidate, dextroamphetamine and modafinil [46, 47].

Alzheimer's disease (AD) is characterised by a progressive amnesic syndrome with the addition of deterioration in at least one other cognitive domain [48]. Pathologically, its hallmarks are intraneuronal neurofibrillary tangles consisting of hyperphosphorylated tau and extracellular parenchymal lesions of amyloid- β plaques, which leads to neuronal loss [49, 50]. Outside of episodic memory decline, traditionally attentional capacity is the first to deteriorate, often preceding impairment in perceptual and language function and reducing a patient's capacity to cope independently [27]. Consistent with pathological distribution, deficits in short term memory, owing to medial temporal lobe involvement, predominate the clinical picture due to the significant

interference with daily activities [51]. Whilst Braak and Braak histopathological staging [52] initially suggested disease emanation from the entorhinal cortex in parallel to brainstem changes, more recent, larger case series have interestingly suggested the pathological process commences in the lower brainstem before spreading to the transentorhinal region [53]. The notion of deficits in attention preceding memory is further supported by longitudinal studies combining neuropsychology and postmortem analysis have shown attention is the first cognitive domain to decline, even before episodic memory, in asymptomatic patients with AD neuropathology compared to asymptomatic patients without AD neuropathology [54]. As AD progresses, attentional domains are affected to different degrees with the most susceptible being executive and orienting domains whilst the alerting domain is usually only affected in more advanced disease [55, 56].

Traumatic brain injury encompasses a diverse range of presentations and a broad spectrum of severity, traditionally classified into mild, moderate and severe depending on Glasgow Coma Scale and post-traumatic amnesia [57]. It is a leading cause of death and disability in young people despite approximately 80% classified as mild. Recently it has become clear that head trauma can lead to progressive neurodegeneration either as a distinct pathological entity known as chronic traumatic encephalopathy (CTE) or as a major risk factor for neurodegenerative disease such as AD [58]. Pathologically, CTE is a tauopathy characterised by deposition of hyperphosphorylated tau in perivascular areas of the cerebral cortex (typically at the sulcal depths), TDP-43 immunoreactive inclusions and neuritis, and a relative absence of amyloid- β deposits [59, 60]. Studies of mild and moderate brain-injured patients, when compared to controls, demonstrated impaired alerting attention as evidenced by slower responses for simple and choice reaction time during the days, weeks and months following injury. Increased standard deviation of reaction times compared to controls suggests greater variability in performance and an inability to sustain alerting attention [61]. Repetitive mild traumatic brain

injury in American football players and jockeys are associated with impaired attention and also problems with executive function and visuomotor speed [62, 63].

Narcolepsy is a sleep disorder characterized by the tetrad of excessive daytime sleepiness, hypnagogic hallucinations, sleep paralysis, and cataplexy often associated with sleep-onset REM periods [64]. The exact pathological mechanism is unknown but it is hypothesised there is autoimmune destruction of the hypocretin-producing neurons of the lateral hypothalamus. These neurons project widely throughout the brain and promote arousal by stimulating histaminergic neurons in the tuberomammillary nucleus, noradrenergic neurons in the locus coeruleus, serotonergic neurons in the raphe nuclei and cholinergic neurons in the basal forebrain [65]. Pharmacotherapy with stimulants is the mainstay of treatment, with modafinil and dexamphetamine as licenced agents.

Attention deficits in psychiatric disease

Psychiatric disorder can also lead to attentional deficits. Schizophrenia presents with positive clinical features such as hallucinations and delusions but also with negative clinical features such as apathy, anhedonia, flattening of affect and attentional deficits [66]. Imaging studies have demonstrated basal ganglia abnormalities in the left globus pallidus, which progress to widespread hypometabolism affecting the frontal lobes, especially the anterior cingulate gyrus and dorsolateral prefrontal cortex [67]. When presented with a visual stimulus, schizophrenics who have never been medicated have a protracted ability to shift their visual attention towards the right visual field; however, shifts towards their left visual field are normal [68]. This finding resolves following medication and is absent in chronic patients [69]. Since posterior parietal lesions are absent in schizophrenia, abnormalities of visual orienting as described above would not be expected unless the frontal lobes/executive attentional network interacted with the parietal lobes/orienting network to affect the initiation of attentional shift [70]. Whilst attentional networks are often considered in isolation, the impact of impairment of one attentional

network on another can be significant yet is seldom explored.

Attention deficit hyperactivity disorder (ADHD) is a developmental disorder characterised by inattention, hyperactivity and impulsivity [71], which are differentially present according to the subtype. Whilst overt behavioural symptoms are dominant in the paediatric population, cognitive inefficiency is more pronounced in adults and centres on executive function and attention [72]. Deficits have been observed in alerting and executive attentional domain tasks with relative sparing of orienting attention [73, 74].

Enhancing attention using diet and lifestyle

Caffeine (1,3,7-trimethylxanthine) is a plant alkaloid naturally found in coffee, chocolate, guarana, and plants such as kola nut, and frequently added in its synthetic form to carbonated drinks [75].

It competes antagonistically at A_1 and A_{2A} adenosine receptors [76], resulting in a slowing of neural activity, and inhibiting the release of neurotransmitters such as glutamate, dopamine, and acetylcholine. Caffeine is a widely used stimulant that has multiple behavioural and physiological effects [77], with consumers often citing psychostimulant benefits after use. A_1 receptors are found in the hypothalamic nuclei, cerebellum, and hippocampus, but are also widely distributed throughout the cerebral cortex [78]. A_{2A} receptors are concentrated in the striatum and regulate perfusion by vasodilation, thus inhibiting psychomotor function. The competitive occupation of these receptors by caffeine increases cerebral perfusion [79], reduces vasoconstriction, enhances psychomotor function [76] and facilitates dopamine release at the presynaptic membrane [80]. A large body of work has suggested that even low doses (20 and 30 mg) of caffeine improve performance on tests of attention as soon as 20 min after consumption [81, 82]. Controversy around caffeine's purported stimulant properties has arisen, however, owing to the failure to take account of withdrawal

effects. Potentially debilitating withdrawal symptoms [83], such as lowered alertness and performance, begin 12 to 24 h after abstinence, peak between 20 and 51 h after abstinence, and vary in severity depending on the regular level of consumption [84]. Typically, withdrawal symptoms last between 2 and 9 days [83]. For example, studies that take withdrawal into account have found that caffeine merely restores cognitive performance during withdrawal up to the level of, but not above, normal levels [84]. There are no randomised trials assessing the effect of acute caffeine on attention in elderly or demented participants and this is an area worthy of exploration.

Caffeine benefits the physical performance of regular consumers and naïve consumers alike [85]. The Institute of Medicine suggest a caffeine dose of 150 mg influences physical performance for up to 10 h [86] and the International Olympic Committee prohibit its use above urinary caffeine concentrations greater than 12 mcg/mL, at which point ingestion is thought to be deliberately for performance enhancement [87]. However, improved physical performance is not thought to be due to enhanced attention but instead mediated via ergogenic effect on aerobic performance [88, 89]. In addition to potential acute therapeutic cognitive and motor benefits, caffeine's chronic effects on adenosine receptors may enhance the neuroprotective role of adenosine [90], although longitudinal data have not demonstrated caffeine to be protective against later life cognitive decline [91, 92].

Compared to caffeine, flavonoids are a relatively new area of interest in the field of dietary attentional enhancers and therefore studies examining cognitive effects are sparse. Flavonoids are found in high levels in green and black teas, grapes, blackcurrants, red wine, apples and cocoa [93]. Cocoa beans are flavanol-rich (a subclass of flavonoid), with epicatechin the main type in unprocessed cocoa [93]. Clinical trials have demonstrated improved attention following flavanol ingestion compared to placebo in a dose-related fashion [94, 95]. A double-blind, controlled, cross-over trial using blackcurrant extracts demonstrated improvement on alerting and orienting but not

executive tasks of attention [96]. This finding, however, has not been consistently reproduced with different flavonoid-rich foods [97]. The mechanism by which flavanols exert their effect is suggested to be via increased cerebral perfusion [93], mediated through stimulation of nitric oxide-dependent vasodilatation [98], commencing after 2 h and returning to baseline within 6 h [99]. Increasing cerebral perfusion and the availability of metabolic substrates to areas of increased cerebral activity is known to enhance cognition. The positive cognition-enhancing effects of ingesting glucose [100] and inhaling pure oxygen [101] when completing cognitively demanding tasks are well established. If further studies continue to support the above proposed mechanism of flavonoid's effect, this could lead to a new line of enquiry into food stuffs rich in nitric oxide e.g. beetroot, which would also potentially improve cerebral perfusion.

Other emerging supplements worth a mention include *Ginkgo biloba*, *Panax ginseng*, *Rhodiola rosea*, theobromine and tyrosine [75]. Limited clinical trials have thus far shown mixed results in most cases and several of these supplements already contain caffeine or flavonoids. Therefore, isolating another active ingredient is challenging. These compounds are currently at the earliest stages of investigation, optimum doses are not known, and mechanisms of action have not yet been definitively established.

Meditation (often termed "mindfulness") has gained increased scientific recognition in recent years as a tool to enhance concentration and cognition. For research purposes meditation can broadly be divided into focused attention meditation (FAM) and open monitoring meditation (OMM) [102]. FAM is the starting point for any novice meditator [103] requiring them to focus attention on a chosen object or event e.g. breathing. The practice of FAM involves alerting attention to a target object, the ability to disengage from a distracting object without further involvement (executive attention) and the ability to redirect focus promptly to the chosen object (orienting attention) [103]. Once familiar with the FAM technique and able to sustain their attentional focus on an object for a considerable amount

of time, a practitioner can then progress to OMM. During OMM the focus of the meditation becomes the monitoring of awareness itself. The aim is to stay in the monitoring state, remaining attentive to any experience that might arise. FAM induces a narrow attentional focus due to the highly concentrative nature of the meditation, whereas OMM induces a broader attentional focus by allowing and acknowledging any experiences that might arise during meditation [103]. A significant shortcoming of the literature arises when comparing studies in that they differ in meditation technique, course prescription, and outcome measure [104]. Study heterogeneity could explain the mixed results of either type of meditation on attention enhancement. Whilst positive studies have demonstrated varying improvement across all of the attentional domains, the effect on alerting attention appears particularly strong [105]. Meditation shows promise as a cost effective, safe attentional enhancer but randomised controlled trials with standardised paradigms systematically assessing short and long term effects are required before firm conclusions can be drawn.

Enhancing attention with prescribed medications

Cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine) were first introduced in 1997 and have now become the first line pharmacological treatment for AD and DLB [106, 107]. They work by inhibiting the breakdown of acetylcholine, an important neurotransmitter associated with memory, by blocking the enzyme acetylcholinesterase. They improve scores on bedside cognitive tests (Mini-Mental State Examination) by a modest 5% over a 12 month period [108]. Whilst attention, working and episodic memory are improved, it is thought an increase in arousal, especially orienting attention, is the common pathway through which these effects are mediated [109].

Amphetamine belongs to the class of drugs called the β -phenylethylamines and is structurally similar to the catecholamine

neurotransmitters noradrenaline and dopamine [110]. The pharmacological effect of amphetamine is predominantly mediated by monoamine release, complemented by reuptake inhibition to augment synaptic monoamine concentrations. Amphetamine dose-dependently increases the extracellular concentrations of noradrenaline in the prefrontal cortex and dopamine in the striatum [110]. D-Amphetamine improved reaction times on the spatial working memory and Stroop tasks for both individuals with schizophrenia and healthy controls, and improved working memory accuracy in schizophrenia [111]. Interestingly, the effect of D-amphetamine in healthy participants is subject to great variation with improved performance only in those subjects who had relatively low working memory capacity at baseline, whereas in subjects who had high working memory capacity at baseline, it worsened performance [112].

Modafinil is a wakefulness-promoting agent licenced by the European Medicines Agency (London, UK) for the treatment of narcolepsy and is also used for the treatment of excessive daytime somnolence. It is thought to have a different mechanism of action than amphetamine, and its use has become widespread due to low risk for abuse and a lower risk of cardiovascular side effects. Modafinil has been shown to directly bind to the dopamine transporter and to the noradrenaline transporter [113, 114]. This leads to significantly elevated extracellular dopamine, noradrenaline, serotonin, glutamate, and histamine levels, and to decreased γ -aminobutyric acid (GABA) levels [115]. Its neural dopaminergic effect is caused by blocking dopamine transporter proteins [116].

Like other stimulants, it increases monoamine release, but also elevates hypothalamic histamine levels, and is therefore considered a 'wake-promoter' rather than an amphetamine-like stimulant [117]. Overall, modafinil is well tolerated, however there are growing case reports of precipitation or exacerbation of psychosis in patients with schizophrenia, narcolepsy and DLB. This is usually associated with doses higher than 200 mg/day or with co-administration of another

stimulant, such as caffeine [118].

Methylphenidate facilitates dopaminergic transmission by inhibiting the dopamine reuptake transporter and is the treatment of choice for ADHD [119]. It inhibits the plasma membrane catecholamine transporters, causing an increase of intrasynaptic dopamine and noradrenaline concentrations [120]. Despite its use as a cognitive enhancer by American college students it is not thought to improve cognition in those with a normal IQ and hence already close to an optimum level of dopamine [119]. It is important to note the effects of dopamine on cognition are often described to follow an inverted U-shaped curve in which intermediate levels of neurotransmitter activity lead to optimal cognitive performance but lower and higher levels may lead to suboptimal performance [109] and that dose–response relationships may vary between cognitive domains [121]. In healthy individuals methylphenidate improves working memory at a medium dose, and speed of processing at a low dose. Improvements in verbal memory, vigilance and executive function have been demonstrated less frequently [121].

Unlike amphetamines, which increase both dopamine and noradrenaline levels in both the nucleus accumbens and the prefrontal cortex, atomoxetine is a selective noradrenaline transporter inhibitor that increases synaptic noradrenaline and dopamine levels in the prefrontal cortex only. The fact that atomoxetine does not increase dopamine levels in the nucleus accumbens (or other striatal regions) [122, 123] may explain the lower liability to abuse (compared to amphetamines) [124]. Clinically, it has been used with success in ADHD [125], improving executive attention [126] but disappointingly efficacy has not been demonstrated in other conditions. Randomised controlled trials of participants with attention deficits following traumatic brain injury [127], schizophrenia with cognitive decline [128], and Huntington's disease [129] did not yield any significant improvement with atomoxetine.

Histamine H_3 receptor antagonists are novel therapies in development to treat daytime somnolence [130]. Histaminergic neurons promote wakefulness through their

direct widespread projections to the cerebral cortex and indirectly via their subcortical targets in the thalamus, basal forebrain, and brainstem. H_3 receptors control the release of a variety of other neurotransmitters involved in sleep-waking regulation, including biogenic amines, acetylcholine, glutamate and GABA [131]. Animal studies have shown a synergistic effect of H_3 receptor antagonists with acetylcholinesterase inhibitors, as they enhance extracellular acetylcholine by distinct mechanisms, which could prove beneficial in DLB patients [132]. So far randomized, controlled, double-blind trials have not yielded any clinical benefit in AD although there was an improvement in one trial for episodic memory but no improvement on tasks of attention [133, 134]. The compound pitolisant has shown great promise in reducing daytime somnolence in narcolepsy in phase II trials, reducing the Epworth Sleepiness Scale by 6 points (max score 24) from baseline, whilst having an acceptable side effect profile [135]. Phase III trial results for pitolisant and other H_3 receptor antagonists are awaited.

Experimental treatments

Deep brain stimulation (DBS) delivers continuous electrical stimulation to focal areas of the brain through chronically implanted electrodes that are programmable in amplitude, pulse width and frequency [136]. Stimulation can alter neurotransmitter release and hyperpolarise or depolarise neurons at the target zone, consequently inhibiting or stimulating neural circuits, respectively. DBS can potentially restore a pre-disease state of activity within a circuit or, alternatively, replace pathological activity with a new therapeutic pattern [137]. High-frequency stimulation of the globus pallidus pars interna (GPi) bilaterally or subthalamic nucleus (STN) bilaterally is an established intervention for advanced Parkinson's disease refractory to medical therapy or associated with motor complication, such as dyskinesias [138]. There is a slight preference for stimulating the STN over the GPi from a motor-efficacy perspective [139]. DBS also impacts on cognition at these sites; whilst there were no large differences in

neuropsychological outcomes after stimulating the two areas, there was a greater negative change on orienting (Trail Making Test B) and executive (Stroop task) tasks of attention with STN stimulation [140]. Epilepsy patients treated with DBS of the bilateral anterior thalamic nuclei were assessed on computerised test of the executive attentional domain both on and off stimulation [141]. There were increased errors relating to lack of response inhibition and increased reaction times when distractors were used, during stimulation periods compared to when stimulation was turned off.

DBS is an exciting, emerging therapy for treating an expanding number of neurological and psychiatric disorders. However, to date very few studies have specifically assessed cognitive modulation as the primary outcome in patients with dementia [142]. A case report of bilateral DBS of the hypothalamus for appetite control in a morbidly obese man failed to achieve the intended outcome although a significant improvement in short term memory was observed [143]. It was hypothesised this unintentional effect was due to stimulation of the fornix, which lies in close proximity and has led to phase 1 trials that have shown encouraging results of a slowed rate of decline in AD [144]. Another case is the report of a man with Parkinson's disease dementia who received bilateral STN electrodes for motor symptoms but also experimental implantation of electrodes into the nucleus basalis of Meynert (NBM) [145]. The NBM is dense with ascending cholinergic neurons important for memory and orienting attention. A substantial cognitive improvement was noted following NBM stimulation, including attention, alertness and concentration, which receded once the stimulation ceased. In addition to STN DBS, bilateral pedunclopontine nucleus stimulation has been explored in six patients with Parkinson's disease dementia who were given low frequency stimulation, which improved attention and executive function. Increased glucose metabolism in the frontal cortices and left striatum following stimulation were also noted [146]. The results from these case reports and small series must be interpreted with caution until data from phase 2 trials become available. As the safety profile of DBS surgery

improves along with the understanding of stimulation effects to salient areas of the brain, then experimental use may become established in promising areas such as the NBM and proliferate to target new areas such as the locus coeruleus, which could improve symptoms of inattention.

Transcranial magnetic stimulation (TMS) involves short-lasting magnetic pulses non-invasively to the cortex of the brain to depolarize neurons. Potential mechanisms for enhancement can be grouped into three classes: i) nonspecific effects of TMS; superficial effects such as coil vibration and audible clicking can prime participants to respond, termed "intersensory facilitation"; ii) direct modulation of a cortical region or network that leads to increased processing efficiency; and iii) disruption or inhibition of non-essential, competing processing (termed "addition-by-subtraction") [147]. Repetitive TMS has inhibitory effects on the cortex when performed at low frequency (< 5Hz) and excitatory effects at high frequencies (> 5Hz) [148]. The major impact of TMS has

been to isolate an area of human cortex *in vivo* and assess its function within a specific cognitive process. This has been illuminating in study of attention, for example, identifying the importance of the right but not the left frontal eye field in supporting sustained attention [149]. Remarkably, TMS can also enhance attention. The right parietal cortex is known to play an important role in top-down modulation of orienting attention. Ten minutes of repetitive TMS to the right posterior parietal cortex [150] reduces the effect of distractors during a visual search task, resulting in reduced reaction time. Similarly, improvement in executive attention and Stroop task performance was seen following anterior cingulate cortex stimulation [151]. While TMS is considerably less invasive than DBS, a significant limitation to TMS therapy is the need for repeated doses by an experienced practitioner to exhibit a chronic effect. Further work to assess the practical application of TMS to improve symptoms and quality of life in chronic neurological disease is awaited.

Conclusions

Attentional enhancers have the ability to improve the quality of life and reduce care costs in people with neurological conditions when impaired attention is a prominent feature. Improved understanding of attention networks has allowed clinicians to target enhancing therapies according to the specific attention domain affected. Unfortunately, few therapies are currently licenced and concerns over side effects are legitimate as, in addition to systemic side effects, imbalances in attention associated with hypervigilance are problematic. Whilst few therapies are currently licenced, novel therapies such as histamine H₃ receptor antagonists, DBS and TMS show promise. There is also the tantalising possibility of self-help for attentional problems through lifestyle changes consisting of dietary modifications and meditation, although further assessment of efficacy and feasibility is required before these can be recommended widely.

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